

European perspectives on quality and non-clinical evaluation of cell based medicinal products



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Centralised Procedure

Rapid and EU-wide authorisation for innovative medicines (210 days)

1 evaluation

1 authorisation

1 product information (SPC, Labelling, PL)

22 languages!



Regulatory framework

Regulation (EC) No 726/2004

Scope

- **Biotechnology Products (Art 3 (1) and point 1 of the Annex)**
 - ❖ **Controlled gene expression (e.g. “transgene”)**
 - ❖ **r-DNA**
 - ❖ **MABs**
 - ❖ **Gene therapy**
 - ❖ **Somatic cell therapy**
(Not Tissue engineered products)
- **New active substance**
- **Orphan medicinal products**



Regulation (EC) No 1394/2007

Advanced therapy medicinal products

- To improve access to ATMPs by increasing the research, development and authorisation of gene therapy, somatic cell therapy and tissue engineered products (TEPs).
- To protect public health;
- To provide legal certainty in order to foster development in the European bioscience industries;
- To harmonise market access in the European Union by establishing a comprehensive regulatory framework for ATMPs.



Regulation (EC) No 1394/2007

- ✓ **Amendment to Annex 1 (Directive 2003/63/EC)**
- ✓ **Traceability**
- ✓ **Long-term follow up of safety and efficacy**
- ✓ **Incentives**
 - ✓ **Scientific Advice on PhV and RMP**
 - ✓ **Fee Reductions (SMEs)**
 - ✓ **Scientific recommendation on ATMP classification**
 - ✓ **Certification of quality and non-clinical data**
- ✓ **Establishment of CAT**
- ✓ **Transitional Period**
 - **Until 30 December 2011**
 - **Until December 2012 (TEPs)**



Regulation (EC) No 1394/2007

Chapter 1 Article 2

(b) Tissue engineered products

- **engineered cells or tissues, and**
 - **regenerating, repairing or replacing a human tissue**
- **A tissue engineered product may contain cells or tissues of human or animal origin, or both. The cells or tissues may be viable or non-viable. It may also contain additional substances, such as cellular products, bio-molecules, biomaterials, chemical substances, scaffolds or matrices**



Regulation (EC) No 1394/2007

Annex 1

Manipulations not considered as substantial manipulations:

- **Cutting**
- **Grinding**
- **Shaping**
- **Centrifugation**
- **Sterilization / irradiation**
- **Filtering / lyophilisation**
- **Cell separation, purification, concentration**
- **Freezing / cryopreservation**
- **Soaking in antibiotic / antimicrobial solutions**



Part IV Advanced Therapy Medicinal Products

Somatic cell therapy medicinal products

- For the purposes of this Annex, somatic cell therapy medicinal products shall mean the use in humans of autologous (emanating from the patient himself), allogeneic (coming from another human being) or xenogeneic (coming from animals) somatic living cells, the biological characteristics of which have been substantially altered as a result of their manipulation to obtain a therapeutic, diagnostic or preventive effect through metabolic, pharmacological and immunological means. This manipulation includes the expansion or activation of autologous cell populations ex vivo (e.g., adoptive immuno-therapy), the use of allogeneic and xenogeneic cells associated with medical devices used ex vivo or in vivo (e.g., micro-capsules, intrinsic matrix scaffolds, bio-degradable or not).**



Regulatory framework -Cells and Tissues-

Directive 2004/23/EC

Standards of quality and safety for donation, procurement, testing, processing, preservation, storage and distribution of human tissue/cells

Directive 2006/17/EC

Technical requirements for donation, procurement testing


Directive 2006/86/EC


Traceability, notification of serious adverse reactions and events, technical requirements for coding, processing, preservation, storage distribution



Regulatory framework -Cells and Tissues-

 **Guideline on human cell-based medicinal products (EMA/CHMP/410896/2006)**

 **Concept paper on the development of a guideline on the risk-based approach according to annex I, part IV of directive 2001/83/EC applied to advanced therapy medicinal products (CHMP/CPWP)708420/09)**

 **Reflection paper on stem cell-based medicinal products (CAT/571134/09)**



Guideline on human cell-based medicinal products (EMA/CHMP/410896/2006)

Scope

- ✓ **Development, manufacturing, quality control, (non)-clinical development of CBMPs**
- ✓ **Intended for products entering the MAA**
- ✓ **Principles to be considered for clinical trials**



Guideline on human cell-based medicinal products (EMA/CHMP/410896/2006)

Risk analysis to be performed at the beginning of the development, based on existing knowledge of the type of product and intended use

- **To identify risk factors associated with the quality and safety of the product**
- **To determine the extent and focus of the data required during non-clinical and clinical development**
- **Basis for the RMP (EMA/CHMP/96268/2005)**



Guideline on human cell-based medicinal products

Quality – Key principles

- **Controlled quality of starting materials**
 - ✓ Cells e.g. primary origin, cell lines (appropriate banking system)
 - ✓ Other material, reagents, excipients (e.g. enzymes, cytokines, antibiotics,)
 - ✓ Matrix, device, scaffold components
- **Validated manufacturing process**
 - ✓ In-process controls,
 - ✓ Batch definition (from sourcing to labeling of final container)
- **Characterization of the CBMP**
 - ✓ Cell purity
 - ✓ Impurities (product or process related)
 - ✓ Adventitious agents
- **Quality control**
 - ✓ Release criteria
 - ✓ Stability



Guideline on human cell-based medicinal products

Quality – Key principles

➤ Potency assay

...based on the intended biological effect which should be ideally related to the clinical response

➤ Traceability (product and patient)



Guideline on human cell-based medicinal products

Quality – Challenges

- **Balance between risks, quality requirements and specific limitations of the cell-based products (e.g. limited sample size, short shelf-life, unique manufacturing process)**
- **Requirement of alternative test methods (e.g. alternative microbiological tests for products with short shelf-life)**
- **Cells themselves bring a variability factor into cell-based products, which may be even increased through other components**



Guideline on human cell-based medicinal products

Non-clinical development – Key principles

- **Conventional requirements not always appropriate, deviation should be justified**
- **To demonstrate proof-of-principle, define the pharmacological and toxicological effects predictive of the human response**
- **Support the intended clinical use e.g.**
 - ✓ **Dose**
 - ✓ **Route of administration and application**
 - ✓ **Identification of parameters for monitoring in patients**
- **Relevant animal model**
 - ✓ **Combined studies (pharm/tox, safety, local tolerance)**



Guideline on human cell-based medicinal products

Non-clinical development – Pharmacology

- Adequate to demonstrate proof-of-principle in a suitable model (in vitro or in vivo)
- Reasonably justified markers of biological activity (in vitro)
- Animal model may include immuno-compromised, knockout or transgenic animals
- Homologous models (e.g. for stem cell differentiation)
- Determination of the minimal or optimal effective amount to achieve desired effect



Guideline on human cell-based medicinal products

Non-clinical development – Pharmacology

- **Kinetics, migration and persistence**
 - ✓ **Conventional ADME studies are usually not relevant**
 - ✓ **To demonstrate tissue distribution, viability, phenotype, trafficking ...**

- **Interactions**
 - ✓ **Cells or surrounding tissue with non-cellular structural components or bioactive molecules**
 - ✓ **Integration of the CBMP with the surrounding tissue**



Guideline on human cell-based medicinal products

Non-clinical development – Toxicology

- **Single and repeat dose toxicity studies/ local tolerance**
 - ✓ **Homologous model**
 - ✓ **Extended observation period**

- **Tumourgenicity**
 - ✓ **Conventional carcinogenicity not feasible**
 - ✓ **Tumourgenicity of host cells and CPMP cells**
 - ✓ **Cells at or beyond limit of routine culturing**

- **Genotoxicity and reprotoxicity case by case**



Guideline on human cell-based medicinal products

Clinical development – Key principles

- **Same principles as for other products apply**
 - ✓ **Directive 2001/20/EC**
 - ✓ **General guidelines e. g. clinical trials, statistic...**
 - ✓ **Specific guidelines**

- **Not classical Phase I to Phase III approach**
 - ✓ **Justification**
 - ✓ **Data driven e.g. non-clinical, clinical experience with the condition**
 - ✓ **Method of application**

- **Long-term follow up**
 - ✓ **Safety**
 - ✓ **Efficacy**

⇒ **Scientific Advice**



Guideline on human cell-based medicinal products

Clinical development – Safety / Efficacy

- **Safety**
 - ✓ **General principles apply**
 - ✓ **The risk of the therapeutic procedure**
 - ✓ **Immune response, infections, malignant transformation**
 - ✓ **Long term safety data**
- **Traceability**
- **Efficacy**
 - ✓ **General guidelines and specific guidelines for the condition to be evaluated**
 - ✓ **Established / validates surrogate endpoints**
 - ✓ **Long term follow up**
- **PhV and RMP**



Thank you for your attention

